COMMENTARY

One hundred and fifty years ago Jonathan Hutchinson published the first data suggesting that male circumcision may be protective against syphilis. He found that among men consulting with a venereal disease circumcised (Jewish) men were less likely to suffer from syphilis than uncircumcised men.[1] About 20 years later Ephraim Epstein, a physician practising in the United States, pointed out that the association between syphilis and male circumcision may be confounded by sexual behaviour—long before ''confounding'' was used in the epidemiological sense of the word.[2] He phrased his concerns as follows: ''In common with others, once I believed that circumcision affords a protection against venereal diseases, but my practice in Vienna, and in this country since 1862 persuaded me fully to the contrary. The apparent immunity which Jews of Russia and European Turkey seem to enjoy from venereal diseases arises from their greater chastity and the practice of early marriage.'' More than a century later the effect of male circumcision on the risk of acquiring sexually transmitted infections (STI), and possible confounding by sexual behaviour became a hot topic of debate. The focus of attention was not syphilis, that deadly STI of the 19th century, but HIV infection the modern deadly STI. Several studies were published that reported an inverse correlation between the prevalence of male circumcision and HIV infection in different regions of sub-Saharan Africa.[3 4] These ecological analyses could not withstand the criticism that they did not allow for differences in sexual behaviour patterns. In 2000 Weiss *et al* published the results of a meta-analysis of 27 studies from sub-Saharan Africa that explored the association between male circumcision and HIV infection, the majority of which controlled for confounding by sexual behaviour. They found that men who were circumcised had a significantly reduced risk of HIV infection, but they felt that ''[the] observational studies in [their] meta-analysis cannot definitively establish a causal role for circumcision in protecting against HIV infection''.[5] Five years later the ''gold standard evidence'' was provided by a randomised controlled trial of male circumcision in men in South Africa.[6] Two more trials are ongoing, one in Kenya and one in Uganda, and the results of these are eagerly awaited.

Here, Weiss *et al*[7] publish another meta-analysis, now on the association between male circumcision and ulcerative STI, including syphilis, chancroid, and HSV-2 infection. The risk of syphilis in circumcised men is substantially reduced, while the protective effect of circumcision against HSV-2 infection is of borderline significance. Assessing the effect of male circumcision on chancroid proved more problematic as there were only a few studies and the ascertainment of the diagnosis of chancroid varied between studies. In four of the seven studies there was a clear association between lack of circumcision and chancroid. What is the relevance of this meta-analysis, considering that syphilis and chancroid are curable STIs? The epidemiological evidence that male circumcision has a protective effect against the acquisition of HIV infection is now very strong, but we are still unclear about the mechanisms of this effect. Hutchinson suggested that circumcision rendered the ''mucous membrane of the glans hard and skin-like.'' Until recently it was believed that this was indeed a possible mechanism.[8] Only in 2000 was an alternative, more plausible explanation proposed: the inside of the foreskin is rich in Langerhans cells that carry CD4 receptors, thus providing an entry point for HIV.[9] More recently, Wawer *et al* have suggested another possible mechanism, one mediated via a local immune response.[10] In addition to a direct protective effect of male circumcision against HIV infection, it is believed that male circumcision also protects ''indirectly'' against HIV infection as it reduces men's vulnerability to ulcerative STIs. The study by Weiss *et al*[7] adds to the evidence that this is indeed a very plausible mechanism. It could also explain why the magnitude of the protective effect of male circumcision against HIV infection varies between different studies and why the protective effect was larger in men with high risk sexual behaviour than in men in the general population.

Further analyses of the data from the South-African trial, and the trials in Uganda and Kenya, should give us more insights into the role syphilis and HSV-2 infection have in the protective effect of male circumcision against HIV infection. We need to know how much of this protective effect is mediated through ulcerative STIs and how much is the result of a direct mechanism, in order to refine recommendations on male circumcision as a public health intervention in populations that are very vulnerable to HIV infection. The data from the South African trial suggest that male circumcision may have an effect on the transmission of HIV, equivalent to that of a vaccine with high efficacy. The trials that are ongoing in Uganda and Kenya will tell us whether these results can also be obtained in populations with different rates of syphilis and/or HSV-2 infection.

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